REMARKS

Claims 5-17 and 19-21 are pending.

Claims 1-4 and 18 have been canceled.

Claims 6, 8-10, 12-15, 17 and 21 stand withdrawn from consideration.

Claims 5, 7, 11, 16 and 19-20 stand NON-FINALLY rejected.

The claims have been amended to more particularly point out and distinctly claim the subject matter Applicants regard as their invention. Support for the amendments is found in the application as originally filed. For example, support for the recitation "human breast cancer cells" is found at p. 42, paragraph 0131. The claims have been amended to use Markush language for the chemical moieties. The claims have also been amended to exclude various substitutions on the phenyl moiety of the arylretinamide genus structure. No new matter has been added.

Applicants respectfully request reconsideration and withdrawal of the outstanding rejections and submit that claims 5, 7, 11, 16 and 19-20 are in condition for allowance.

Pursuant to the election of specie requirement set forth in Office Action mailed June 27, 2005, the compound corresponding to R_2=OH, R_3=H, R_4=NO_2, R_5=H and R_6=H has been searched and examined for patentability. In other words, Applicants elected the specie shown in Example 26 (see pp. 33-34)(which is Compound No. 18) of the instant specification being an arylretinamide di-substituted on the phenyl moiety with *o*-hydroxy and *p*-nitro. As such, the arguments set forth herein are with respect to the instantly claimed compound and methods of use thereof.

In the Office Action mailed December 19, 2006, claims 5, 7, 11, 16 and 19-20 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Chem. Abst. 130:232097 to Clifford et al. (CA'097) or Chem. Abst. 134:65874 to D'Ambrosio et al. (CA'874) in view of DE 2,300,107 to Konig et al. Regarding DE 2,300,107, reference herein by Applicants is made to the English language equivalent embodied in GB Patent Specification 1,449,027 (GB'027). Regarding CA'874, reference herein by Applicants is made to the full journal article, D'Ambrosio SM et al., Differential Response of Normal, Premalignant and Malignant Human Oral Epithelial Cells to Growth Inhibition by Chempreventative Agents, *Anticancer Research* 20:2273-2280 (2000). ("D'Ambrosio"). Regarding CA'097, reference herein by Applicants is made to the full journal article, Clifford JL et al., Retinoid Receptor-dependent and -independent Effects of N-(4-Hydroxyphenyl)retinamide in F9 Embryonal Carcinoma Cells, *Cancer Research* 59, 14-18 (January 1, 1999). ("Clifford").

In the instant Office Action mailed May 10, 2006, it is argued that DE 2,300,107 "disclose[s] the equivalency of unsubstitution to nitro, alkyl, alkoxy, etc. substitution on the phenyl moiety of similar anti-cancer retinamides." (P. 3). The Office Action also asserts that DE 2,300,107 "does teach an arylretinamide disubstituted on the aryl moiety (s. claim 4)." (Id.)

Applicants respectfully submit that GB'027 fails to teach equivalency of substituted and unsubstituted phenyl moieties in retinamide compounds. GB'027 discloses only substituted phenyl moieties including

> phenyl substituted by one or more lower alkyls of 1 to 4 carbon atoms, such as methyl, ethyl, propyl, butyl or isobutyl, halogen, such as fluorine, chlorine, bromine or iodine, nitro, alkoxy, such as methoxy or ethoxy, or carbalkoxy, such as ethoxycarbonyl or methoxycarbonyl.

(P. 1, lines 27-30)(See also p. 1, lines 15-19). GB'027 makes no mention (implicitly or explicitly) of equating substituted and unsubstituted phenyl moieties. Thus, Applicants respectfully traverse the assertion that GB'027 teaches or suggests equivalency of substituted and unsubstituted phenyl moieties in vitamin A acid amide compounds.

As regards di-substitution of the phenyl moiety in a vitamin A acid amide compound, the only di-substituted compound that GB'027 discloses is vitamin A acid 3,4-dimethylanilide (see claim 5, p. 7, line 49), whereby the phenyl moiety is di-substituted with methyl groups. (See also p. 2, line 32, whereby the R^1-N- R^2 amine sustitutient may be 3,4-dimethylaniline). The instantly claimed invention expressly excludes such di-methyl substituted phenyl moieties.

At p. 3 of the Office Action mailed June 27, 2005, it states that CA'097 discloses N-4-hydroxyphenylretinamide (i.e., 4HPR) and that CA'874 discloses "N-(3-hydroxyphenyl)-retinamide and N-(2-hydroxyphenyl)retinamide to have anti-tumor properties." Applicants note that D'Ambrosio discloses various mono-hydroxy and mono-carboxy substituted phenyl retinamides. (See p. 2274, first column). The instantly claimed invention expressly excludes such mono-hydroxy and mono-carboxy substituted phenyl retinamides.

The instantly claimed invention is patentably nonobvious over Clifford, D'Ambrosio and GB'027. Clifford, D'Ambrosio and GB'027 fail (alone and collectively) to render the instantly claimed invention *prima facie* obvious under 35 USC § 103(a) because, *inter alia*, there is no implicit or explicit motivation to combine the references and make the instantly claimed di-substituted *p*-nitro, *o*-hydroxy-phenyl retinamide compound. Clifford and D'Ambrosio only teach mono-hydroxy and mono-carboxy substituted phenyl moieties. The

relevant portions of GB'027 disclose the following phenyl substitutions: 3,4-dimethyl, *m*-nitro, *p*-fluoro, 2-methyl, 4-ethocycarbonyl, 2-methoxy, *p*-ethoxy, *p*-chloro, and *m*-chloro. In addition, none of the references teach or suggest implicitly or explicitly the instantly claimed *p*-nitro substitution on the phenyl moiety.

Thus, as regards the instant elected specie, D'Ambrosio discloses *o*-hydroxy phenyl retinamide (i.e., 2HPR), GB'027 discloses *m*-nitro phenyl retinamide, and GB'027 discloses *m,p*-dimethyl phenyl retinamide. Applicants simply fail to discern any permissible motivation, implicit or explicit, in the references to make the claimed di-substituted *p*-nitro, *o*-hydroxy-phenyl retinamide compound or use said compound to induce apoptosis in human breast cancer cells or human breast cancer, particularly given the unpredictability of cancer science generally and therapeutic activity of vitamin A analogs.

Moreover, even if the elected compound was *prima facie* obvious over the references, the instant specification provides secondary indicia of nonobviousness in terms of unexpected bioactivity as compared to the prior art compound 4HPR. At pp. 43-44, Table 1, it shows that Compound No. 18 (i.e., the elected compound) had ">50% the activity" of 4HPR, which is the compound disclosed in D'Ambrosio. Clearly, the elected compound and methods thereof are unexpectedly superior and patentably nonobvious.

Moreover, Applicants respectfully submit that the full scope of claims 5, 7, 11, 16 and 19-20 are patentably nonobvious for at least the same reasons set forth herein respecting the elected specie.

For the foregoing reasons, Applicants respectfully submit that the instantly claimed invention is patentably nonobvious over prior art of record, and Applicants request reconsideration and withdrawal of the obviousness rejections.

In the Office Action mailed December 19, 2006, claims 19 and 20 are rejected under 35 U.S.C. § 112, First Paragraph as being nonenabled. (P. 3). It states that

> [t]he specification does not enable any person skilled in the art to reasonably treat all tumors, leukemias, etc. Treating cancer is well known to be highly problematic. Although the level of one of ordinary skill in the art is high, in vitro cell line toxicity is not recognized as a sufficient predictor of in vivo results. The specification shows only in vitro cell line toxicity data, but the art accepted models are animals with xenogenic tumors. Undue experimentation would be required to determine which of applicant' [sic] compounds are suitable for treating which tumors.

(Id.)

Applicants respectfully submit that no supporting documents, prior art or the like has been made of record to support judicial notice of such assertions. Applicants respectfully

traverse any such assertions of judicial notice. Applicants further submit that the art is replete with *in vitro* use of MCF-7 cells to screen for induction of apoptosis and breast cancer activity. (See, e.g., paragraph 0130-0131 of instant specification). Applicants also traverse the characterization of the instant data as mere "toxicity" data. In Table 1 of the instant specification, the column heading "growth[a] inhibition" clearly sets forth activity data for the elected specie. (See footnote stating "[a]activity vs. 4-HPR standard, all at 10^{-5}M: ++ = >50% the activity of standard.").

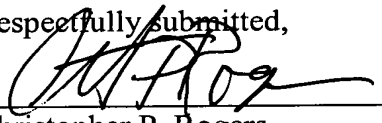
Instant method of use claims 19 and 20 have also been amended to recite "human breast cancer." Instant Example 26 and Table 1 clearly demonstrate that the elected specie is enabled and has substantial utility. (Spec. at pp. 33-34 and 43-44). Moreover, the full scope of claims 19 and 20 are also enabled and have substantial utility as demonstrated by the 45 working examples set forth in the instant specification.

For the foregoing reasons, Applicants respectfully submit that the instantly claimed invention is patentably enabled, and Applicants reqeuest reconsideration and withdrawal of the nonenablement rejections.

In view of the remarks made herein, Applicants respectfully request reconsideration of claims 5, 7, 11, 16 and 19-20 and that a timely Notice of Allowance be issued in this case.

The Commissioner is authorized to charge any fees under 37 CRF § 1.17 that may be due on this application to Deposit Account 17-0055. The Commissioner is also authorized to treat this amendment and any future reply in this matter requiring a petition for an extension of time as incorporating a petition for extension of time for the appropriate length of time as provided by 37 CFR § 136(a)(3).

Respectfully submitted,



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